Current Review

Can vitamins prevent neural tube defects?

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A recent six-centre clinical trial has shown that the risk of a neural tube defect in 429 infants born to women who had already had a child with such a defect and had taken a simple multivitamin and mineral supplement during the next pregnancy was only 0.7%, compared with 4.7% in 510 infants born to women who had not taken the supplement.[1-3] If it is confirmed that a reduction of over 80% in the risk of these severe congenital defects can be produced by a widely available and inexpensive nutritional supplement, this is one of the great medical advances of the century. But are these results reliable?

Neural tube defects, which include spina bifida, anencephalus and some rarer abnormalities, are among the commonest severe congenital defects in developed countries. Spina bifida, a major cause of childhood disability, has a catastrophic effect on the family and a considerable economic impact on the community. Progress in medical intervention into these conditions has depended not only on scientific developments but also on ethical, legal and economic factors. Thus, while the prognosis of spina bifida was improved greatly during the 1950s and early 1960s by control of infection, early surgery, and control or prevention of hydrocephalus by drainage valves for the cerebrospinal fluid, this soon led to open discussion of whether treatment was always justified and the declaration by Lorber[4] and Illingworth[5] that the full technical possibilities of medical intervention should not always be used. This judgement was followed by decreased survival of infants born alive with spina bifida between the late 1960s and the 1970s.[6,7] In the late 1970s the discovery that α-fetoprotein concentrations are increased in the amniotic fluid surrounding infants with open neural tube defects, along with the ethical, the social and particularly the legal changes making abortion acceptable to society, led to the development of prenatal detection systems. The use of amniocentesis and ultrasonography to detect neural tube defects in women who have had a previously affected baby is now routine.[6,8,9] In areas of high incidence, such as parts of the United Kingdom, population screening by estimation of the serum α-fetoprotein level in early pregnancy has been implemented.[10,11] This is a much less accurate and more expensive system than testing only high-risk women, and is less attractive in areas of lower incidence, such as Canada.[12-14]

Incidence of neural tube defects

Primary prevention has always been the ultimate objective of epidemiologic research into neural tube defects, although until recently this appeared to be merely a distant hope. These defects are to some extent familial, the risk to siblings of affected children ranging from 2% (in Canada) to 5%.[15] Neural tube defects are the only major congenital abnormality more common in girls, with about two thirds of infants with anencephalus and 60% of those with spina bifida being female.[6] However, more than any other major congenital defect, the incidence (or, more precisely, the prevalence at birth) of neural tube defects varies between and within countries, particularly for predominantly Caucasian populations. Within Canada the incidence of the defects varies threefold, generally decreasing from east to west, a pattern not shared by any other major defect.[6,16] This great variation suggests a primarily environmental cause.

The conditions have also shown marked variations in incidence over time. A remarkable epidemic occurred in New England. Rates of anencephalus and spina bifida combined rose from about 3/1000 births in the early years of this century to almost 10/1000 in the 1930s, and then dropped back to around 3/1000 again by the 1960s.[17] Eastern Canada's higher rates have decreased over the last 20 years, whereas in western Canada the lower rates have been relatively stable.[6,16]

Could there be dietary factors?

Two epidemiologic features have been regarded as consistent with a dietary etiology: the greater incidence of defects in infants born to women of the lower socioeconomic groups;[6,18] and, perhaps more indirectly, the seasonal variation, with the highest rates in babies conceived in the spring. The latter trend is clearer in data from the 1950s than in recent data.[6,19] The social class gradient may reflect the poorer diet of less advantaged women, and the seasonal variation, which does not fit with trends known for any infectious disease, may reflect imbalances in fresh foods, which might be most marked toward the end of winter.[20]

There have been few large and well designed analytic studies. To

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study prospectively etiologic factors in even a common congenital defect requires extremely large-scale studies: several thousand women must be investigated during pregnancy to obtain information for a reasonable but still small number of women whose babies have defects. Retrospective studies comparing women who have already delivered or have been found to carry an affected baby with mothers of unaffected babies are much easier and require smaller numbers of individuals, but they are open to major errors in recall bias. Several retrospective studies have suggested that mothers of affected babies have a lower quality diet, defined in various ways, but the results of all the studies have been difficult to interpret because of major potential biases in ascertainment.[21,22]

In a case–control study reported in 1965 by Hibbard and Smithells[23] women who had delivered babies with neural tube defects were found to have a folate deficiency post partum compared with mothers of normal babies. Subsequently Smithells and colleagues[24] performed a prospective study in which blood was taken in the first trimester from over 1000 women; it demonstrated that the 6 women who subsequently gave birth to infants with neural tube defects had lower mean erythrocyte folate and leukocyte ascorbic acid concentrations than the women who had unaffected babies.

Trial by Smithells and colleagues

Since further observational studies appeared unlikely to refute or confirm a dietary hypothesis, Smithells and his colleagues chose a hypothesis-testing experimental trial. They decided that it would be wise to supplement the diet of women who had already had a child affected with a neural tube defect and who were intending to undergo another pregnancy. As the association between a possible dietary deficiency and these defects was by no means certain they felt a randomized trial would be appropriate. However, their proposal was turned down by the ethics committees of several of the participating institutions,[25] presumably because the committees regarded the scanty and indirect evidence for the protective effect of vitamins available at that time to be sufficient to make a randomized trial incorporating a "no treatment" arm unethical.

Thus, the published report relates to five, later increased to six, centres in the United Kingdom at which women who had had a baby with a neural tube defect were seen when considering a further pregnancy. It was recommended that the women take a multivitamin and iron preparation for not less than 28 days before conception and to continue taking it to at least the date of the second missed menstrual period.[1,2] Those who were already pregnant or who refused to take part were regarded as the control group. One tablet of the suggested supplement, Pregnavite Forte F (Bencard), to be taken three times a day, provided 4000 IU of vitamin A, 400 IU of vitamin D, 1.5 mg of thiamine, 1.5 mg of riboflavin, 1 mg of pyridoxine, 15 mg of nicotinamide, 40 mg of ascorbic acid, 0.36 mg of folic acid, an amount of ferrous sulfate equivalent to 75.6 mg of elemental iron, and 480 mg of calcium phosphate.

Of the 429 infants born to women who took the supplement during the specified period 3 (0.7%) had a neural tube defect, compared with 24 (4.7%) of the 510 infants born to women who did not take the supplement. The difference was highly statistically significant. The risk of a neural tube defect for infants born to women who had already had an infant with a neural tube defect and who did not take the supplement was similar to that usually seen in British studies.

The results of the trial by Smithells and colleagues were dramatic. The risk of a neural tube defect in the infants of the treated women was about one seventh that in the control group and only slightly greater than the risk for infants of women who had not previously had an infant with such a defect. Such a low risk might be generally regarded as acceptable, thus making counselling and screening unnecessary. Perhaps the most exciting prospect developing from the trial is that if vitamin supplementation prevents the defect in the offspring of women who are highly predisposed to have such children, surely improvement in diet by similar vitamin supplementation in the general population could dramatically reduce the total occurrence of the defect.

Assessment of study design

But are the results reliable? Medicine is replete with examples of mistakes being made by reliance on inadequately controlled trials, and Smithells and colleagues' study group was not randomized, was not double-blind and had no placebo component, thus failing to provide three key aspects of design that are often regarded as essential.

No particular design specification should be taken as the only criterion for truth. Consider the criticisms that the trial by Smithells and colleagues was not double-blind and did not use a placebo. The purpose of the double-blind, placebo approach is to prevent a true action of the agent under test from being confused with psychologic or other ill-defined effects on the outcome or on the ascertainment of this outcome by the patient or the investigator. But recognizing a neural tube defect in an infant is hardly a point of contention and should be free from bias, both of the mother and of the investigator. Some might claim that psychologic mechanisms could play a part in the etiology of such a severe and striking anatomic defect, but it does not seem likely that those who took the supplement felt so differently about their pregnancy that their psychologic state would be greatly improved.

The lack of randomization of the two groups of women compared is a more serious matter. Clearly, the groups may have differed in a number of important variables. The group that did not take the supplement had a less favourable distribution of social class and included a considerably larger number of women from Northern Ireland; both low social class and residence in Northern Ireland are risk factors for birth of an infant with a neural tube defect. The risk of a neural tube defect in a subsequent pregnancy among women who already have an infant with such a defect also varies by social class,[26] but no direct information on how it varied between the cities included in the trial by Smithells and colleagues is available,

though one might expect a similar gradient. Since variations in recurrence risk follow those expected from a polygenic pattern of inheritance, the risk being approximately the square root of the incidence rate in the population,[6] a given factor, such as social class, will be associated with a smaller proportional variation in recurrence risk than in incidence rate. The observed differences in measured factors between the two groups do not "explain" the difference in outcome in a statistical sense; for example, there was a significant difference in outcome between the women who took the supplement and those who did not in the Northern Ireland group alone.[3]

However, the experimental and comparison groups of women may have varied in other ways as well. One hypothesis is that the women who elected to accept the recommendation for vitamin supplementation differed from the comparison group in other aspects of diet, not only because of differences in socioeconomic status but because of conscious attention to diet. No dietary assessment or biochemical assay of nutrients was performed in the study. One of the difficulties in accepting the dramatic effect on recurrence risk is a natural incredulity that such a small degree of supplementation would produce such a dramatic effect. If, however, the difference between the two groups is not merely the three tablets a day of vitamin supplement but a more major difference in diet, then perhaps the results become more biologically plausible. Whether this matters is an interesting question. One could argue that if advice to use a vitamin supplement is always accompanied by other changes in diet that lead to a greater improvement in total nutrient intake, then that simply reinforces the importance of the primary intervention. However, the link between taking supplements and making other dietary changes is likely to change in different circumstances, and so it is important to understand the mechanism of the supplementation effect.

The most usual assumption is that folic acid is the active agent, both because of the earlier work and because of the results of a small trial of folic acid alone in southern Wales, in which a nonsignificant decrease in the recurrence risk was seen among women who had been randomly assigned to receive 4 mg of folic acid daily compared with those who had taken a placebo.[27] However, it has been suggested that the active ingredient of the multivitamin and mineral supplement could be vitamin D,[28] vitamin B_{12}[29] or vitamin C, the last perhaps enhancing the excretion or degradation of solanidines, which are teratogenic for hamsters and are found in potatoes.[30,31] Thus, a link has been postulated with an earlier hypothesis — that neural tube defects are related to the consumption of blighted potatoes.[30,31]

Direct action or further research?

A major disagreement has arisen inside and outside the medical profession about the appropriate action to be taken in the light of the results of Smithells and colleagues' trial. The question is whether the results should be regarded as sufficiently conclusive to lead to direct action or whether further research is needed.

Those suggesting direct action are supported by the strength of the association in the trial done by Smithells and colleagues and argue that all women who have had an affected infant and are considering a further pregnancy should be advised to take the vitamin supplement. It would have to be accepted that we have no information as to which component of the preparation is important, and that perhaps the effect is not due to the vitamin supplement itself but to other conscious or unconscious changes the woman may make if we persuade her that nutrient intake is important for her future pregnancies. Those who believe that such an intervention is justified discount these scientific niceties as irrelevant compared with the very dramatic reduction in risk that could accrue, and they conclude that any further trial in which a group of women at risk receive less than the supplementation used in the earlier work would be unethical, although they support further studies to specify the nature of the preventive action.

On the other hand, many authorities argue that the trial of Smithells and colleagues has given insufficient evidence to support a policy decision to initiate a program that presumably will continue indefinitely. They base their arguments on specific criticisms of the study, such as those outlined above, and on the general feeling that major policy decisions should never be based on the results of nonrandomized studies or on the results of one study.

Two proposed studies

Thus, further research is needed. The direct approach is to set up larger scale, randomized studies of high-risk women (those who have already had an affected baby) that could offer opportunities to distinguish between different components of the intervention. Two such studies have been started. One, developed by the British Medical Research Council (MRC), is a double-blind study of 2×2 factorial design[32] in which women are randomly assigned to receive one of four possible supplements: folate and other vitamins plus minerals (as used in the trial of Smithells and colleagues); folate and minerals; other vitamins and minerals; and minerals only. For an adequate sample size, between 1000 and 2000 women will be required, and it is hoped that the study will be carried out in 20 centres, with patient accrual occurring over a few years. The inclusion of a group receiving minerals but no vitamins is presumably to avoid the challenge that a true "no treatment" group would be unethical, but this still may be an untreated group as it has rarely been suggested that the minerals were the effective component of the supplement used in the trial by Smithells and colleagues.

The second trial has been started in Dublin, where the strong Roman Catholic tradition makes antenatal diagnosis and abortion unacceptable. This is a three-arm trial, with women receiving multivitamins and folate, folate only or multivitamins only.

MRC trial unethical?

Several authors have been outspoken in their criticism of the MRC trial, largely on the basis that the existing evidence is so strong that such a trial is unethical.[33-35] The

language has, on occasion, been strong, with one author employing quotations from the Nuremburg war crimes trials on the use of humans for experimentation.[33]

It has been pointed out that if the ethics committees examining the proposal for the multicentre trial several years ago found the concept of randomized allocation unethical, surely it is even more unethical in the light of the results of Smithells and colleagues' trial. Alternatively, one could argue that the decision of the original ethics committee was in error on the basis of the extremely slim and indirect evidence at that time and that the current ethical and scientific problems result from the lack of a randomized trial initially.[36] Ethical committees themselves are under no scientific or ethical review, and whether the results of their deliberations have a net positive or negative role on science and society has not been assessed.

The responses of the MRC have not been above criticism. In November 1982 the journal *Nature* went to press with a blank space because the MRC had put pressure on two contributors to withdraw their letters to *Nature* that dealt with the proposed MRC trial.[32,37]

Prevention on a wider scale

Neither those suggesting an immediate policy decision nor those suggesting a further trial have intensively considered primary prevention of the 95% or more of neural tube defects that occur in the infants of women who have not previously had an affected child. This is a much bigger problem. It can be argued that offering vitamin supplementation to the relatively small number of women who have already had an affected baby is a simple and fairly cheap measure; however, implementing a policy aimed at prevention on a wider scale would be much more complex. It is useless to wait until the first antenatal visit. If the defects can be prevented by early vitamin supplementation, then such supplementation would have to be administered to all women at risk of becoming pregnant, which suggests intervention through public education or at family planning clinics, active publicity directed at all young women, and improvement in certain basic and ubiquitous foodstuffs. The potential risks and costs would then increase. Certain components of the original multivitamin preparation, notably vitamin A, have the potential for toxic effects, and while this admittedly small risk may be acceptable to a woman who has a substantial risk of having a baby with a defect, it would hardly be acceptable if the supplementation were to be aimed at all women of reproductive age.

As well as the ethical questions of a trial, there is also the practical issue of patient recruitment if, as seems to be apparent, a large number of physicians feel that the evidence favouring vitamin supplementation is strong. Ways of acting on the evidence presented and simultaneously attempting further assessment could be considered. These include actively introducing a policy of offering supplementation to all women in a defined population who have had affected babies and setting up an active registry of all such women and monitoring the recurrence rate. If the results of Smithells and colleagues' trial are correct and the recurrence rate in women taking such a supplement is one seventh of that in those not taking the supplement, the effect should be clear even without an appropriate control group, and the recurrence risk of all women in the target population, those taking the supplement and those not taking it, will be lower than the previous risk or the risk in similar groups to whom the policy has not been applied. Difficulty would arise if the recurrence rate were only somewhat lower than expected, perhaps 2% to 3%. Such rates have been reported in North American studies and may be the expected rates in the United Kingdom in the future in view of the current decrease in the incidence of the defects in the population.[38] In addition, now is the time to consider ambitious plans for trials of primary prevention before that too becomes a difficult issue. In a country such as Ireland that has a very high rate of these defects, the possibility of setting up a mass program to supplement the diets of all women of reproductive age in certain areas of the country and then comparing the incidence rates of neural tube defects in those areas and other areas could be considered.

Unexplained variation

The key issue is the interpretation of a striking difference between two self-selected groups of women who differed in whether they took the supplement offered. Do we assume the relation is causal because we cannot demonstrate a precise alternative explanation, or do we assume it is not causal because the results of nonrandomized studies are inherently unreliable? This issue has been discussed in many medical contexts, and illustrations of striking differences between nonrandomized but apparently similar groups are worthy of attention. Recently MacCarthy and coworkers[30] summarized results from a descriptive study of the risk of neural tube defects in Dublin women who had already had an affected infant. The women were divided according to the hospital in which they had delivered their first affected infant. The recurrence rates for the four hospitals were 0.6% (1/157), 4.6% (6/130), 6.2% (4/65) and 10.3% (19/185). The statistically significant differences in these rates were as large as those in the trial by Smithells and colleagues. MacCarthy and coworkers could suggest no reason for the differences, and this type of unexplained variation should make us very cautious about accepting the results of nonrandomized studies.

Conclusion

We are left with individual and societal choices. To suggest to a patient that taking $20 worth of vitamins might prevent a tragedy and seems very unlikely to be harmful is easy. To then argue that therefore all women with a previously affected child, and perhaps all women likely to become pregnant, need multivitamin supplementation is less easy; small individual risks and costs are magnified. Is this another penicillin or polio vaccine or another diethylstilbestrol or high-dose oxygen situation? Reluctantly, I conclude that we need better evidence on efficacy and on safety.

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